REMARKS CONCERNING THE AMENDMENTS

The above amendments have been made in an effort to more clearly define a narrower scope of the present invention and to place claims into immediate condition for allowance.

Claims 1-4, 8, 10, 27, 28 and 30-53 have been cancelled.

Claims 5-7, 9, 11-26, 29 and 54 - 64 are in condition for allowance.

New Claims 54-64 find antecedent basis in the original specification, original claims 41-44, claim 5 as amended, and the like.

Amendments to existing claims include clarifying or preferred limitations (e.g., "proton MR spectroscopy" and "nonviability" versus "inviability," which concepts find clear antecedent basis in the original specification.

SUMMARY OF THE OFFICE ACTION

1) Claims 5-7, 9, 11-26 and 29 have been rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) in view of Palti (US Patent No. 5,190,041)

2) Claims 20-22 have been rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) in view of Palti (US Patent No. 5,190,041) in further view of Johnson et al. (US Patent No. 6,051,208)

3) Claim 24 has been finally rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) in view of Palti (US Patent No. 5,190,041) and further in view of Dinsmore (US Patent No. 6,140,116)

ARGUMENTS IN RESPONSE TO THE REJECTIONS

Claims 5-7, 9, 11-26 and 29 have been rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) in view of Palti (US Patent No. 5,190,041)

Claim 5 will first be discussed to emphasize specific limitations (not to the exclusion of others) that are particularly material to differentiation from this combination of references. Claim 5 recites:

> A **method for indicating viability of transplanted progenitor or stem cells** grown in a culture, the method being performed with a medical device that supports at least one sensing function, the method comprising:
>
> non-destructively observing a region of a patient to where progenitor or stem cells grown in a culture have been transplanted;
>
> **sensing a property within said region of a patient that is indicative of cell viability or nonviability of transplanted progenitor or stem cells** grown in a culture; and
>
> **using data from sensing said property** within said region **to indicate cell viability** from a transplant of progenitor or stem cells grown in a culture within the region **wherein said cell viability is indicated by a property in cell chemistry resulting from an event selected from the group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function, specific cell dysfunction, volumetric expansion of cell population, and volumetric decrease of cell population**.

It is asserted that in Column 1, line 16 through column 2, line 16; column 3, line 28 through column 4, line 45; and column 10, lines 22-55 that Lemelson teaches "monitoring the viability of the tissue condition in response to the growth factor." This is not seen to be the actual content of the Lemelson disclosure. As noted from a complete quotation of this disclosure from Lemelson, the disclosure actually describes the use of imaging to guide the delivery of cells and materials expected to produce beneficial results on the cells. There is no monitoring of sensing properties of cell responses as recited in the claims, especially no sensing of such cell responses as chemical responses as recited in some of these claims. The Lemelson disclosure is presented below, the highlighted

portions emphasizing that Lemelson does not disclose the recited format of monitoring cell response.

Column 1, line 16 – column 2, line 16 (Lemelson)

In accordance with the invention, a computer controlled injection needle is employed to inject a therapeutic agent into select target tissue of a patient, for example, a tumor. The tumor is located using one or more scanning modalities capable of distinguishing the target tissue such as plain view X-ray, computerized axial tomography X-ray (CAT scanning), magnetic resonance imaging (MRI scanning), positron emission tomography (PET scanning), and ultrasound scanning. Once the target tissue is located and its borders defined by the imaging modality, location coordinates are generated and assigned with respect to a support structure supporting the patient. A manipulator arm assembly under computer control is used to move and operate the injection needle. **A stored program, having user defined parameters and the location coordinate data, then directs the injection needle to a plurality of sites on the patient's body at corresponding insertion depths which result in positioning the tip of the injection needle into the target tissue at various locations. The therapeutic agent is then injected in controlled amounts at each such injection location**. In this manner, the agent may be delivered to the target tissue with greater precision than with prior methods so that less of the therapeutic agent is delivered to non-target tissue where its effects may be deleterious.

The present invention may also be employed with therapeutic agents for effecting tissue engineering, that is the selective growth of various cell types within a target tissue of a patient. One such embodiment uses an agent comprising a growth factor or cytokine in conjunction with another agent for creating specificity. A growth factor may then be employed to cause the selective growth of specific living tissue via cellular proliferation without causing the undesired proliferation of other cell types normally responsive to the growth factor. Growth factors which can be used with such method include those of broad specificity such as EGF, PDGF, fibroblast growth factors (FGFs), hepatocyte growth factor (HGF), insulin, insulinlike growth factor (IGF-1), nerve growth factor (NGF), vascular endothelial growth factor (VEGF), and macrophage colony stimulating factor (M-CSF). Such method may be useful not only in treating certain disease states where specific cellular proliferation is of value, but also in enhancing the production of animal products such as milk from dairy cattle and various hormones from genetically engineered animals.

In order to produce such a selective growth agent, a specific growth factor or other cytokine is selected which elicits a desired response (eg., cellular proliferation) in a specific target cell of a multicellular organism. Monoclonal antibodies are then produced which have a specific binding affinity for other cells of the organism that also respond to the growth factor, which other cells are referred to herein as non-target cells. Such monoclonal antibodies are directed toward antigenic determinants that are expressed by non-target cells but not by

target cells. The monoclonal antibodies are then conjugated with a protein corresponding to the extracellular domain of the growth factor receptor. In order to eliminate the response of the non-target cells to the growth factor, the monoclonal antibody conjugate is administered together with the growth factor by employing the computer controlled injection needle apparatus as described above. The antibody conjugate then binds to the non-target cells and presents a binding site for the growth factor that results in competitive inhibition of the growth factor's binding to the cell's native growth factor receptor. The target cells, on the other hand, are left fully responsive to the growth factor. The method may also be combined with other techniques for causing tissue growth such as electrical stimulation, used presently for promoting bone healing, as well as specific nutrients needed for cell growth.

As can be readily seen, there is **ABSOLUTELY NO DISCLOSURE OF MONITORING CELL RESPONSE AS RECITED IN THE CLAIMS.**

Column 3, line 28 through column 4, line 45 (Lemelson)

"**The location coordinates of select tissue of a living being into which select tissue a therapeutic agent** (such as a drug, genetic material, a selective growth factor composition, or a transplant medium containing cellular transplants) **is to be injected are defined or computed with respect to images of the patient's anatomy** defining anatomical structures which may be generated, for example, by employing computerized axial tomography (CAT scanning), magnetic resonance imaging (MRI), ultrasonography, PET, infrared or microwave imaging, or other types of electronic scanning. In accordance with the present invention, a computer image of a select anatomical area is generated by using one or more of such conventional imaging modalities. A location coordinate with respect to a patient support structure is assigned to each pixel making up the image. **The antatomical region into which it is desired to deliver the therapeutic agent is then located on the electronically generated image or images by a radiologist**, for example, with selected of the pixels making up the image of the region serving to define the transplant location. A preferred means by which this can be performed is to display the images on a display monitor having a manually positionable cursor for outlining an area containing the lesion. The operator of the system then inputs to a computer digital data in the form of codes defining the anatomical location to which a cellular transplant or transplants are to be delivered as represented by the select pixels within the outlined area. As described below, each pixel of the body or organ image displayed by the computer has assigned to it a set of location coordinates calculated or defined with respect to a structure, such as a table supporting the patient, while the imaging is performed. The same or a similar patient support structure is then utilized during the injection procedure, **the injector or injection needle is carried in movement by the manipulator or catheter under computer control, inserted into select tissue, and operated so as to deliver the agent to select location coordinates with respect to the support structure.** In a typical

embodiment, a first computer program calculates the location coordinates of select body regions as defined by pixels of images produced by **an imagining device using coded signals representing the sensed relative prositions of the patient support in the imaging device, while a second computer program calculates the location coordinates of the injection needle and determines when the needle is located in the select body region into which it is desired to deliver the therapeutic agent**.

"In one form, the patient is required to be in the same position with respect to the support structure during both the imaging and injection procedures so that the location coordinates selected will correspond to the proper anatomical region of the patient. One way of accomplishing this is to use a patient support structure having a moldable support structure defining a surface that can be made to conform to the shape of the patient's body as a kind of body cast. Once such a body impression is made, the patient may be placed in substantially the same position on the support structure for both scanning/imaging and subsequent transplantation procedures. Such a moldable patient support may also serve to immobilize the patient during both procedures. Other patient retraint devices, such as straps and adjustably positionable table stops, may also be employed.

"The manner of assigning location coordinates to each image pixel depends upon the particular imaging modality. For example, with a conventional CAT scanner, the x-ray tube emits a narrow beam of x-rays toward the patient with an x-ray detector, such as an array of scintillation detectors, positioned on the opposite side of the patient on which an x-ray shadow is formed. The x-ray tube and detectors, mounted on a rigid gantry, are rotated in multiple steps about the body until an entire axial slice is viewed from multiple angles. Codes defining the data acquired by the scintillation detectors are entered into a computer which uses mathematical algorithms operable to reconstruct a cross-sectional image of the region examined. Such a computerized scanning arrangement calculates the degree to which the tissue interposed between the x-ray tube and the detectors absorb the x-ray beam and thereby provides an attenuation coefficient for each area of tissue examined. Essentially, the quantity of x-rays absorbed in small volumes(voxels) of body tissue in the slice is computed. Computer analysis of the data collected then allows assignment of a numerical value to each small area (pixel) of the cross-sectional plane. By means of a digital-to-analog converter, the numerical value of each pixel is translated to a gray scale value for driving a CRT display or the like."

Again, as can be readily seen, there is **ABSOLUTELY NO DISCLOSURE OF MONITORING CELL RESPONSE AS RECITED IN THE CLAIMS.**

Column 10, lines 22-55 (Lemelson)

"In the replication of unicellular organisms, where each cell division generates a new individual, proliferation is controlled by the type and supply of nutrients in the medium in which the organisms reside. In the growth and

replication of multicellular organisms, on the other hand, the component cells thereof must obey strict control parameters that limit their proliferation in order to produce and maintain the intricate organization of the multicellular body. At any point in time, most of the cells in a multicellular organism may be in a resting, non-proliferative state even though the supply of nutrients are plentiful. The cells of a multicellular organism are intrinsically unable to divide unless they are provided with positive signals from other cells. Many of these positive signals are in the form of cytokines and growth factors which bind to complementary receptors in the plasma membrane of responsive cells to stimulate cell proliferation via a signal transduction pathway. In this way, the negative controls that otherwise restrain growth are overridden.

"Most cytokines and growth factors are proteins, although non-protein growth factors also exist, such as steroid hormones which act on intracellular receptor proteins. As of the date of this application, over fifty such protein growth factors have been discovered, and they can be divided into broad and narrow specificity classes. Factors with broad specificity, such as platelet-derived growth factor (PDGF) and epidermal growth factor (EGF), affect many classes of cells. Thus PDGF acts on a number of target cells including fibroblasts, smooth muscle cells, and neuroglial cells. EGF, while acting mainly on epidermal cells, also acts on many other cell types. At the other extreme are narrow specificity growth factors such as erythropoietin whose sole action is to induce proliferation of red blood cell precursors."

This section of Lemelson deals only with background information on the nature of growth factors. Again, as can be readily seen, there is **ABSOLUTELY NO DISCLOSURE OF MONITORING CELL RESPONSE AS RECITED IN THE CLAIMS.**

At an absolute minimum, the rejection fails from the fact that there is absolutely no teaching in Lemelson (**as asserted**) that there is monitoring of the viability of implanted cell. As that teaching is absent, all rejections based on the assertion of this teaching in Lemelson are in error and must be withdrawn.

A more detailed analysis of Lemelson is also provided here. The Lemelson U.S. Patent No. 5,865,744 reference cited by the examiner (which was also cited as prior art in this patent application) discloses methods for using MRI and other imaging technologies to deliver drugs and cellular transplants to a patient under the control of a computer. Lemelson does not disclose delivery of progenitor or stem cells as recited, and most importantly does not monitor the cells for viability as recited in the claims. Nonetheless, the examiner asserts that "Lemelson's use of growth factor materials and cells as transplant agents to proliferate cell or tissue growth is equivalent to the intended purpose

of the claimed invention in current application". However, contrary to the examiner's assertion, , there is no monitoring of the cell response to the introduction of these materials. Further contrary to the examiner's assertion, image-guided delivery of progenitor and stem cells imposes delivery and monitoring requirements that are not covered or anticipated by Lemelson's patent. For example, since embryonic stem cells are in an early and often undifferentiated stage of development, they are more susceptible than other cells to environmental and physiological factors, including trophic factors at the site of cell placement and the techniques used for cell delivery. It is generally known that conventional catheter-based techniques for intracerebral delivery of cells, such as those disclosed by Lemelson, can provoke inflammatory tissue reactions, hemorrhage, necrosis, and degeneration and are therefore not suitable for delivering stem cells. Traumatic changes at the implant site can compromise cell survival or disrupt the ability of the implanted embryonic stem cell implant to form viable functional nerve connections with existing neurons in the brain. Such cytoarchitectural changes can be monitored with high-resolution MRI methods, such as anisotropic diffusion coefficient mapping and diffusion tensor imaging, as disclosed by the Applicants but which are not taught by Lemelson.

Although Lemelson describes the use of MRI and CT to initially position the "therapeutic material" at target locations in tissues, he does not provide any method or device that enables the monitoring of the distribution of injected drugs or the migration of implanted cells over time. It is well established in the medical literature that stem cells have a propensity to migrate from the site of implant to remote locations. It is also known that stem cell migration is influence by trophic factors and pathophysiologic changes, such as ischemia. Thus, it is important that the present application provides an imaging method that can monitor cell migration and eventual in situ localization of implanted stem cells. Monitoring of cell migration by MRI is not currently possible without the use of techniques such as catheter-based RF microcoil imaging or the use of cells labeled with an MR-visible label, which are disclosed in the present application (claims 13-16) but are not taught by Lemelson.

The present application may be further distinguished from the teachings provided by Lemelson on the basis that certain claims expressly provide for a quantitative assessment of various parameters related to cell viability, as follows:

- an imaging means for quantitating the number of cells implanted into a tissue in a human body.
- an imaging means for quantitating the number of living cells implanted into a tissue in a human body.
- an MR imaging means for quantitating the number of cell-to-cell membrane contacts in a cell implant in a tissue in a human body.
- an MR imaging method for quantitatively determining the apparent diffusion coefficient in a population of living cells implanted into a tissue in a human body.
- an MR method for quantitatively determining the pH and fluid-electrolyte parameters in a population of living cells implanted into a tissue in a human body.
- an MR method for quantitatively determining the phosphorus and water proton metabolites in a population of living cells implanted into a tissue in a human body.
- an MR imaging means for quantitating the functional capillary density of the tissue region contiguous with the cell implant.

Although the Lemelson reference describes a method "to predetermine the quantity and rate of flow of transplant medium or medication pumped to the injector," neither Lemelson nor Palti discloses an imaging means for quantitatively assessing physiologic and metabolic parameters of progenitor or stem cell implants that can non-invasively determine cell viability.

The Examiner admits that "Lemelson does not disclose indicating viability by determining from a group consisting of cell activity, cell inactivity, cell growth, cell death, specific cell function and dysfunction, volumetric expansion of cell population and volumetric decrease of cell population." It is now well established that poor implant survival is a key limitation to establishing transplant efficacy. Recent studies report that 80-95% of embryonic stem cells die within 48 hours after implantation. Moreover,

surviving implanted cells may re-innervate only 25% of the host brain tissue and only at 25% of normal density. Published studies of embryonic stem cell implants have shown a 10- to 100-fold variability in cell survival and in graft volume. Pathophysiologic changes at the implant site that compromise cell survival, such as reduced blood flow, increased tissue pH, and abnormal tissue concentrations of ions and neurotransmitters can be monitored using the MR imaging and spectroscopy methods disclosed by the applicants, but which are not even addressed in the Lemelson patent. Real time MR imaging at higher Tesla fields, such as disclosed by the applicants, can provide images identifying concentration changes of these introduced and production-stimulated materials, particularly by using RF microcoils in the region where the therapeutic agents are delivered.

The presently claimed technology in this application in particular discloses methods to monitor non-invasively the ongoing viability of the cell implant in terms of whether the cells are adequately perfused by the local microvasculature. Unlike the Lemelson reference, the present invention also discloses (and in some claims recites) a method for quantitating the functional capillary density in the anatomic region of the cell implant, for quantitatively determining the metabolic status of a population of living cells implanted into a tissue, and for the MR-assisted quantitation of molecular level changes in composition of the cell implant.

Lemelson does not provide any quantitative method for monitoring the physiologic and metabolic status of the cell implant. The present invention, by comparison, provides an MR imaging method for controlled quantitative delivery (i.e., actual number of cells) into tissues of living cells and cell suspensions. The invention additionally discloses an imaging system to monitor the metabolic status of the transplanted cells and their assimilation into their tissue transplant environment based on quantitative MR indicators of cell growth and proliferation. The present invention provides a method by which metabolic changes arising from cell replication or cell death can be quantitatively measured using localized proton lactate and metabolite signals, and the resulting MR data provide a non-invasive quantitative assessment of cell viability.

Palti is cited as disclosing the fact that "implanted cells are detectable by imaging method to determine concentration over a period of time, which in turn determines the

growth characteristics, increasing or decreasing which is due to cell death or proliferation (Col. Col. 2, line 63- col. 4, line 43; col. 4, line 65 – col. 5, line 13." Because of the length of the first citation, only portions thereof will be completely analyzed below and the Examiner is invited to point out any descriptions therein which are felt to be more relevant.

First it is to be noted with Palti, that the function of the invention is to monitor blood glucose levels, not cell viability. (See the Abstract, first sentence, Field of the Invention and the quoted portion from the Detailed Description of the Invention:

> **The present invention relates to means for monitoring the level of glucose in blood and bodily tissues** Particularly, the invention relates to **a system for monitoring glucose with glucose sensitive cells that produce an electrical response to glucose levels in their surrounding medium** which is then used to determine the blood glucose level, to administer insulin or to take other measures to alter the blood glucose level such as diet adjustment.

Column 4, line 65 through Column 5, line 13 (Palti)

> FIG. 1 schematically describes one embodiment of a system of the present invention which is described in further detail below. As shown at the upper right of FIG. 1, glucose diffuses from the bloodstream into the extracellular space in bodily tissues. Eventually the glucose diffuses to implanted glucose sensitive cells which are a part of the system of the present invention. The implanted cells respond by exhibiting electrical activity, such as a change in membrane potential, commensurate with the concentration of glucose in the extracellular space.
>
> The electrical activity can be detected or monitored in one of two ways. Where the electrical activity is strong enough to be detected through a body surface (e.g., layers of skin), the electrical activity is detected directly by an external signal sensor. Alternatively, the electrical activity is monitored by an implanted signal pickup device. The pickup device processes and amplifies the electrical activity The amplified signal is then transmitted through a body surface (such as the skin) and is detected by the external signal sensor.

This section describes monitoring glucose functions, not cell viability.

Col. 2, line 63- col. 4, line 43

In accordance with the present invention, systems are disclosed which utilize implanted glucose sensitive living cells to monitor blood glucose levels by monitoring glucose levels in bodily tissues in which the glucose level is in equilibrium with that of the blood. In this respect, the implanted cells are similarly situated to endogenous insulin secreting glucose sensitive cells. The implanted cells produce a detectable electrical or optical signal in response to changes in glucose concentration in surrounding tissue **The**

signal is then detected and interpreted to give a reading indicative of blood glucose levels. This reading can then be used as a basis for altering insulin or other drug dosage for injection, as a basis for giving instructions to an external implanted insulin pump to alter the amount of insulin delivered by the pump, or as a basis for taking other corrective measures, such as altering diet. As a result, blood sugar levels can be more closely monitored and controlled in a noninvasive way and insulin dosage can be more closely tailored with concomitant control of symptoms associated with diabetes.

A system for monitoring tissue and blood glucose level is disclosed which comprises glucose sensitive cells which are capable of producing a signal in response to changes in glucose concentration in the medium surrounding the cells. The signal produced can either be electrical or optical. In certain embodiments, the cells are contained in a capsule which is constructed from a membrane or similar substance which is impermeable to antibodies, yet permeable to nutrients to keep the cells alive. The capsule can also be fitted with means for collecting the signals produced by the cells.

In instances where the signal is electrical, these collecting means can be metal electrodes which are placed in contact with the cells such that the signal produced by the cells can be measured as a potential difference between the electrodes. The system can further include an implanted signal pickup device which is connected to the electrodes in the capsule for processing (e.g., amplifying and modulating) the signal for later transmission through the body surface, such as the skin, or for transmission to an external or implanted insulin pump. Once the signal is processed the pickup device passes the signal on to means for transmitting the processed signal In other embodiments, the implanted cells produce an electrical signal which can be detected by external electrodes without employing electrodes in the capsule or an implantable signal pick-up device.

In instances where the signal is optical, the signal is produced by a change in the optical qualities of the cells or specifically the membranes of the implanted cells. Preferably, the signal is produced by dyes contained within or coated on cellular membranes which will change the optical properties of the cells in response to changes in electrical activity of the cell. This change in optical quality can be detected through relatively transparent body surfaces, such as thin skin layers or fingernails. Alternatively, the optical change can be measured by an implanted optical detector which processes the detected signal much as the implanted pick-up device previously described processes electrical signals. The processed signal can be used to control an insulin pump or transmitted through the skin for external detection.

The electrical signal or the optical signal are detected through the skin by an external sensor and then correlated to a corresponding blood glucose level. The sensor includes means for detecting the signal, means for processing such signal and correlating it to the corresponding blood glucose level, and output means for reporting or relating the blood glucose level as determined.

Alternatively, the implanted signal pickup device can pass a processed signal on to an implanted insulin pump, which, in response to such signal, delivers an appropriate dosage of insulin corresponding to the determined blood glucose level.

Capsules for use in practicing the present invention are also disclosed which comprise a membrane which is impermeable to antibodies and is permeable to nutrients necessary for cell growth. Glucose sensitive cells are enclosed within the membrane, along with electrodes in contact with the cells such that changes in the electrical activity of the cells can be detected as a potential difference between the electrodes.

Alternatively, in place of the electrodes, the capsules can enclose means for "shorting-out" the interior of the capsule with respect to the exterior of the capsule such that the electrical activity of the cells is optimally dissipated on the exterior of the capsule. As a result, the electrical activity will be maintained at a level which can be detected by appropriate sensing means.

Capsules are also disclosed which contain glucose sensitive cells which have been treated such that the cellular membranes of the cells are coated with dyes which are sensitive to change in cellular membrane potential.

Finally, methods of monitoring the blood glucose level employing the capsules and systems of the present invention are disclosed. Basically, those methods comprise implanting into the patient glucose sensitive cells, detecting the signal produced by the cells in response to levels and/or changes in glucose concentration and correlating that signal with the corresponding blood glucose level. Methods of administering glucose are also disclosed which comprise administering a level of insulin (or other correcting agent) appropriate to the blood glucose level determined in accordance with the methods disclosed herein. Such insulin can be either administered manually or by operation of an external or implanted insulin pump which is connected to the detecting and monitoring system. It is understood that other therapeutic agents which will alter blood glucose levels, such as those sold under the tradenames "Dia Beta" (glyburide; Hoechst -Roussel), "Glucontrol" (glipizide; Pfizer) and "Diabinese" (chlorpropamide; Pfizer), can be substituted for insulin as described herein.

The Rejection apparently makes at least two assumptions that are not supported by the disclosure. First, Palti gives no teaching, instruction or suggestion that cell viability for implanted cells is being sensed and monitored. The sensing of the activity of the glucose-responsive cells is not being monitored for their viability, **and that is never suggested**, but rather the glucose-responsive cells are being monitored to secondarily infer the functionality of glucose regulating cells. Without denigrating the technology of Palti, the absence of a separate ability to monitor to the glucose-responsive cells is a flaw in the Palti system, as a lack of sensed change in conductivity and the like could be based upon either changes in the insulin-producing cells, changes in the glucose-responsive cells (which are never considered by Palti) or other environmental/system changes (such as bacteria that metabolize glucose). As Palti does not teach what it is asserted to teach and Lemelson fails to teach what it is asserted to teach, the combination of references cannot be found to teach what is asserted in the rejection. The claims cannot be obvious

under this ground of rejection based upon these references and what has been asserted as their teachings in the rejection.

THE REJECTION IS COMPLETELY IN ERROR AND MUST BE WITHDRAWN

Additionally, as recited in certain others of these claims, neither the Lemelson or Palti references disclose how metabolic changes in implanted progenitor or stem cells can be quantitatively measured by non-invasive *in vivo* proton spectroscopy with local or volume RF-coils to obtain quantitative proton observable metabolites such as GABA, PCr, creatine, choline, and lactate. The quantitative feature of the present application is important because concentrations of lactate above 2-6 millimolar indicate a significant occurrence of dying or dead cells. Thus, unlike Lemelson and Palti, the present application describes how viable cell implants can be distinguished from dead or dying cells based on quantitative regional indications of lactate to metabolite levels.

The present application also discloses how non-invasive imaging technologies can track, in vivo, C-13 labeled glucose introduced directly into brain tissues together with the cell implant. Glucose metabolism in the cell implant is assessed by observing the resulting quantitative data from in vivo conversion of the C-13 labeled glucose into C-13 labeled metabolic by-products. The levels and turnover rates of glucose utilization, as measured by the concentrations of the converted compounds, reflect the ongoing viability of the cell implant. Thus, the methods disclosed by the applicants can be distinguished from the Palti patent in which glucose sensitive cells are implanted into tissue to function as surrogate 'glucodetectors' in patients with insulin-dependent diabetes.

Claims 20-22 have been rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) in view of Palti (US Patent No. 5,190,041) in further view of Johnson et al. (US Patent No. 6,051,208)

The sole feature asserted to be added to the teachings of Lemelson in view of Palti is the use of hyperpolarized gas in MRI imaging. Even assuming that the Johnson reference teaches this to be obvious, the teachings of Johnson et al. fails to overcome the fatal deficiencies described above with regard to the combination of Lemelson in view of Palti with respect to claims 5 et seq. This rejection must fail for at least those reasons.

Claim 24 has been finally rejected under 35 USC 103(a) as unpatentable over Lemelson (US Patent No. 5,865,744) in view of Palti (US Patent No. 5,190,041) and further in view of Dinsmore (US Patent No. 6,140,116)

The sole feature asserted to be added to the teachings of Lemelson in view of Palti by Dinsmore is the use of methods to detect at least one of choline, NAA, GABA, phosphocholine and creatine. Even assuming that the Johnson reference teaches this to be obvious, the teachings of Dinsmore fails to overcome the fatal deficiencies described above with regard to the combination of Lemelson in view of Palti with respect to claims 5 et seq. This rejection must fail for at least those reasons.

All rejections have been traversed and overcome by these arguments.

CONCLUSION

Applicants believe that the application and claims are now in proper order and in condition for allowance. **If the Examiner believes that any issues remain that can be resolved by an Examiner's Amendment, the Examiner is respectfully requested to call the attorney of record.** Please direct any inquiries to the undersigned attorney at (952) 832-9090.

Respectfully submitted,

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CERTIFICATE UNDER 37 C.F.R. 1.8: The undersigned hereby certifies that this Transmittal Letter and the paper, as described herein, are being deposited in the United States Postal Service, as first class mail, with sufficient postage, in an envelope addressed to: MAIL STOP: AMENDMENT, BOX 1450, Commissioner for Patents, Alexandria, VA 22313-1450 on 27 JULY 2005.

Mark A. Litman
Name

Signature